10. THE MOLECULAR MECHANISMS OF SCHIZOPHRENIA FROM GLIAL CELLS PERSPECTIVE

9.3 PSYCHOSIS BIOTYPES VERSUS CLINICAL SYNDROMES THROUGH THE PRISM OF INTRINSIC NEURAL ACTIVITY

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Background: Deviation in level of intrinsic neural activity (ongoing brain signals recorded with EEG/MEG) is observed in psychosis. Neurophysiological models have proposed this physiological indicator as a genetically mediated core deviation in psychosis. Translational models of intrinsic activity deviations promise to identifying multiple distinct physiological mechanisms for psychosis manifestation. Intrinsic activity deviations may masquerade as higher levels of neural response in sensory cortices, but ultimately may lead to poor signal-to-noise ratios, particularly when psychosis cases are required to identify stimulus salience.
Why do we not hear more about intrinsic activity as a core biomarker for any psychosis variation? An explanation is provided by the current project. The Bipolar-Schizophrenia Network for Intermediate Phenotypes (B-SNIP) published a means for categorizing psychoses by neurobiological homology via use of multiple biomarkers (psychosis Biotypes) rather than by clinical features. B-SNIP demonstrated the superiority of Biotypes versus DSM diagnoses for capturing neurobiological similarity through multiple external validating measures (social functioning, measures of brain volume from structural magnetic resonance images, clinical diagnoses and biomarker features among first-degree relatives). Independent analyses since the initial publication have provided additional support for the usefulness of psychosis Biotypes.
Methods: For this project, we analyzed ongoing neural activity from 64 EEG sensors during 150 intervals of 10 sec duration from over 1450 B-SNIP subjects. These data (never before published) were from the intertrial interval (ITI) of an auditory paired-stimuli task used in Biotypes construction (these ITI data themselves were not used). Although the subjects were engaged in a task (counting the number of stimulus pairs), the data used here were not part of the task itself. Data were evaluated for single trial power (estimate of neural response strength on individual trials) as a function of frequency of neural oscillations (from 2–50 Hz) over the whole head. Data were then averaged over single trials to yield an estimate of the overall strength of nonspecific (unrelated to sensory processing) neural activity.
Results: When evaluated by DSM diagnoses (schizophrenia, schizoaffective disorder, bipolar disorder), the 95% confidence intervals for all groups overlapped the healthy group means across all frequencies. When considered by psychosis Biotypes, differences were obvious and statistically significant. In comparison to healthy persons, Biotype-2 probands (the most neurophysiologically activated subgroup in previous analyses) were notably high on nonspecific neural activity, and Biotype-1 probands (the most cognitively and neurophysiologically compromised subgroup in previous analysis) were notably low. Group separations on this metric were better than those obtained with original intrinsic EEG measure used in psychosis Biotypes construction, indicating this more pure intrinsic activity measure is capturing a meaningful component of Biotype neurophysiology. This was true across a range of oscillatory frequencies for the probands. The first-degree relatives of the Biotype probands showed similar patterns, although higher frequency oscillations (above 20 Hz) better differentiated relatives from healthy persons.
Discussion: Intrinsic activity deviation is a promising biomarker for translational research programs aimed at differential treatment development, but using DSM psychosis diagnoses would obscure its importance for understanding psychosis.

9.4 COMPLEX SYSTEM THEORY AND THE TRANSDIAGNOSTIC USE OF EARLY WARNING SIGNALS TO FORESEE THE TYPE OF FUTURE TRANSITIONS IN SYMPTOMS

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Background: Recently, we showed that assumptions from complex system theory seem applicable in the field of psychiatry. This means that indicators of critical slowing down in the system signal the risk for a critical transition in the near future. In the current study we wanted to explore whether the principle of critical slowing down may also be informative to anticipate on the type of symptoms that individuals are most likely to develop. This is relevant as it may lead to personalized prediction of risk of whether adolescents with mixed complaints are most likely to develop either depression, anxiety, somatic or psychotic symptoms in the near future. For example, we hypothesized that critical slowing down in feeling 'suspicious' more strongly indicates risk for a future transition to psychotic symptoms, while critical slowing down in feeling 'down' more strongly indicates risk for a transition to depressive symptoms.
Methods: We examined this in a population of adolescents (most between 15 and 18 years) as adolescents are an at-risk group for the development of psychopathology. At baseline experience sampling was performed for 6 days, 10 measurements a day. Affect items were used to assess autocorrelation as an indicator of 'critical slowing down' of the system. At baseline and follow-up SCL-90 questionnaires were administered. In total, 147 adolescents participated both in baseline and follow-up measures and showed increases in at least one of the defined symptom dimensions. We examined whether autocorrelation was positively associated with the size of symptom transition and whether different type of transitions (in depression, anxiety etc.) were differentially predicted by autocorrelations in specific affect states.
Results: The analyses were done very recently, and findings have not been presented before. We found both shared and specific indicators of risk in the development for transition to various symptom dimensions. First, autocorrelation in 'feeling suspicious' appeared to be the strongest signal for all assessed psychopathology dimensions (SCL-90 depression: std beta: 0.185; $p < 0.001$; SCL-90 anxiety: std beta: 0.093; $p=0.006$; SCL-90 interpersonal sensitivity: std beta: 0.176, $p<0.001$). Second, we found that the combination of 'feeling suspicious' and the affect with the second-highest autocorrelation together predicted the precise type of symptom transition. Thus, the combination of feeling suspicious (std beta: 0.185; $p<0.001$) and down (std beta: 0.108; $p=0.001$) predicted larger increases in depressive symptoms one year later on the SCL-90, while the combination of feeling suspicious (std beta: 0.093; $p=0.006$) with feeling anxious (std beta: 0.086; $p=0.014$) predicted larger increases in anxiety symptoms a year later on the SCL-90.
Discussion: These findings support the hypothesis that indicators of slowing down can not only be used to predict risk for a mean level shift in symptoms, but that they can also be informative for the type of symptom transitions at hand. In a next step these findings could be translated to designs measuring personalized early warnings for future direction of symptom shifts, and if successful to clinical implementation of these techniques.

10. THE MOLECULAR MECHANISMS OF SCHIZOPHRENIA FROM GLIAL CELLS PERSPECTIVE

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Overall Abstract: In the past decade, rapid advances in the field of neuroscience resulted in a dramatic paradigm shift in the way we understand the role

of glia in normal brain functions and brain disorder pathology. A growing body of evidence shows that diversified populations of astrocytes, microglia, oligodendrocyte precursors and mature oligodendrocytes play a critical role in the regulation of synaptic functions, blood-brain barrier, immune response regulation, myelination and axonal conduction, and in the synthesis of the extracellular matrix, a key regulator of neural plasticity. Building on this evidence, exciting new findings are beginning to emerge, shedding light on glia abnormalities in schizophrenia and their impact these functions. This symposium aims to discuss and integrate the current state of knowledge on direct evidence for glial abnormalities in schizophrenia and their underlying mechanisms.

Dr. Juliana Nascimiento will present novel findings on the effects of NMDAr antagonists and antipsychotics influence glial cell lines and 3D cultures as neurospheres and cerebral organoids. Results from these studies point to the central role of glycolysis, EIF2 signaling and translational machinery in oligodendrocytes and astrocytes. Dr. Paul Klauser will report on elegant investigations on the implication of developmental redox imbalance inducing oxidative stress leading to impairments of oligodendrocytes, myelin formation and eventually to the disruption of white fibers integrity and conductivity, especially in brain regions where the metabolic demand is high. In patients, alterations of white matter were found to be inversely correlated with blood levels of GSH precursor cysteine and could be prevented by the early administration of the antioxidant N-acetyl cysteine. Dr. Sabina Berretta will discuss recent findings on novel modalities of interaction between glial cells, extracellular matrix and neurons, postulated to affect synaptic structural plasticity and axonal conductance. A growing body of evidence from her group shows disruption of such interactions in schizophrenia, potentially contributing to synaptic pathology and impacting neural connectivity. Dr. Dost Ongur will build on previous work showing abnormal diffusion of neuron-specific metabolite NAA in frontal white matter in patients with chronic schizophrenia in the absence of abnormalities in the diffusion of non-specific metabolites Cr and Cho. State-of-the-art recent studies on first episode psychosis patients and matched healthy controls show that NAA diffusion is normal in first episode patients but Cr and Cho diffusion is abnormal, suggesting that white matter abnormalities in non-neuronal elements in early phases of schizophrenia which are followed by neuronal damage in chronic disease.

10.1 STEM CELL-DERIVED IN VITRO MODELS FOR DEPICTING THE ROLE OF GLIA IN SCHIZOPHRENIA FROM A PROTEOMIC PERSPECTIVE

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Background: A number of basic and translational studies have clearly indicated the vital role of glia in brain function and the pathophysiological mechanisms of neuropsychiatric disorders, including schizophrenia. The difficulty on studying the molecular basis of glial cells in vivo, led to the development of animal models, which are considered the gold standard to this type of understanding. However, the inherent difficulties in establishing these models for psychiatric disorders and the simplicity of in vitro models, especially given the recent advances in stem cell-based technologies have driven the development of sophisticated in vitro models, which may be attractive for studying the molecular basis of schizophrenia.
Methods: Here, we report our investigations in terms of proteome while establishing protocols to generate human pluripotent stem cells-derived cerebral organoids as well as human cerebral organoids-derived astrocytes and oligodendrocytes.
Results: The proteome of cerebral organoids show major proteins from neuronal cells as expected, but also several glial markers, supporting the notion that glial cells may be obtained out of these organoids. Besides, the proteome of three schizophrenia and three control organoids have been investigated. Proteins found are broadly distributed on functional activities such as cell growth and maintenance, energy metabolism and cell communication and signaling, and are correlated to cortical brain tissue. We also succeeded in isolating astrocytes out of cerebral organoids. These cells are under investigation in terms of molecular differences associated to schizophrenia.
Discussion: The generation of brain organoids and isolation of astrocytes and eventually oligodendrocytes hold great potential for the investigation of the role of glia in schizophrenia, providing an useful approach to drug screening and disease modeling, as our results showed in schizophrenia- and control-derived cells. Additionally, proteomics adds knowledge about information and connections being formed into these models.

10.2 REDOX DYSREGULATION, OLIGODENDROCYTES AND WHITE MATTER ALTERATIONS IN SCHIZOPHRENIA

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Background: Widespread (Klauser et al., 2016) and progressive (Cropley et al., 2017) cerebral anomalies of white matter diffusion properties (i.e. fractional anisotropy, FA) have been observed in the Australian Schizophrenia Research Bank (ASRB), one of the largest samples of patients with schizophrenia. From a topological perspective, widespread alterations of white matter tend to concentrate into hub regions that interconnect brain areas over long-distances in a so-called "rich-club" (van den Heuvel et al., 2013; Klauser et al., 2016) in which the metabolic demand is high and thus are most likely to suffer from oxidative stress. Evidence from human and animal models suggests that redox dysregulation leading to oxidative stress during neurodevelopment is implicated in schizophrenia pathogenesis (Steullet et al., 2017). At the cellular level, the triad composed of NMDAR hypofunction, neuroinflammation and dopamine dysregulation interacts with redox imbalance and leads to oxidative stress, affecting oligodendrocytes precursor cells (OPC) and parvalbumine interneurons (Steullet et al., 2016). However, the links between redox imbalance, oligodendrocytes and gross alterations of white matter integrity are largely unexplored. Under oxidative stress induced in vitro by impairing the synthesis of glutathione (GSH), the key player in antioxidant defense, OPC showed a decreased proliferation mediated by an upregulation of Fyn kinase activity. In the prefrontal cortex of a mouse model with impaired GSH synthesis, mature oligodendrocyte numbers as well as myelin markers were decreased at peripuberty (Monin et al., 2014). FA was also reduced in fornix-fimbria and anterior commissure, a change accompanied by a reduced conduction velocity (Corcoba et al., 2015).
Methods: 49 patients with psychosis and 64 healthy controls were scanned with the same 3-Tesla scanner. The diffusion spectrum imaging (DSI) sequence included 128 diffusion-weighted images with a maximum b-value of 8000 s mm−2. White matter diffusion properties were estimated using generalized fractional anisotropy (gFA). Total blood cysteine (Cys, protein-bound form, free reduced and free oxidized form), the rate-limiting precursor of GSH, was measured by high performance liquid chromatography from plasma samples collected at the same time-point as MRI brain scans.